REMARKS

Claims 18-24 are now pending. A "clean" list of the now pending claims is provided above. Amendments to the claims are indicated in the section entitled "Version Showing Changes Made" which follows the present section.

Claim 18 has been amended to state that the first step involves forming a a functional Kir3.0 channel. Support is found, for example, at page 7, line 19 to page 2 and page 8, line 27 to page 9, line 6.

Applicants acknowledge the withdrawal of the previous rejections under 35 U.S.C. § 112.

Objection to the Specification

The specification is objected to for lack of agreement between the figure legends and the drawings. As the Examiner points out, the drawings are informal. Formal drawings will be submitted after a finding of allowable claims. Amendments to make the description agree with the formal drawings will be made upon the determination of the format and submission of such drawings and the finding that the application is otherwise allowable. Applicants respectfully request that this objection be held in abeyance until such time.

Obviousness-Type Double Patenting

Claims 18-20 are rejected under the judicially created doctrine of obviousness-type double patenting over claims 1-19 of USPN 5,734,021 (the '021 patent) in view of Yatani et al. *Science* 235:207-211, 1987 (Yatani).

The standard for an obviousness-type double patenting rejection is the same as for a rejection under 35 U.S.C. § 103 (*see* MPEP § 804), except that only the claims and not the underlying disclosure of the issued patent may be considered as prior art. Therefore, for this rejection to be proper, the claims of the '021 patent and Yatani must 1) disclose each element

of the presently claimed invention; 2) provide motivation to combine and modify these teachings to obtain the present invention ; and 3) provide a reasonable expectation of success in obtaining the present invention. These criteria are not met in the present rejection.

Claim 18 is directed to a method of screening for agents that inhibit the activity of a Kir3.0 channel by forming a functional Kir3.0 channel from at least two different polypeptides, combining the channel with a candidate agent under conditions permitting K+ current and measuring the current. Claims 19 and 20 depend from Claim 18 and, therefore, also have each of these elements.

Yatani describes patch clamp recording from heart cell membranes and manipulation of G-proteins. Yatani does not disclose forming any channels, but rather, merely records from endogenous membrane channels.

The present Office Action states that the reasons for this rejection are set forth in the previous Office Action (Paper No. 12, mailed 3/12/00). The rejection cited states, "Claims 1-19 of U.S. Patent No. 5,734,021 teach the method of modulating the Kir3.0 channel current activity." (Page 3, third full paragraph). Applicants submit that it is not possible to properly respond to this rejection, because the '021 patent only has five claims, which claims are directed to KGA channel proteins. These claims do not disclose the methods asserted. Claims 1-19 of U.S. Patent No. 5,744,324 do disclose methods of modulating KGA channels. However, Applicants have already submitted a terminal disclaimer to this patent.

In addition, the present Office Action states that the present Claim 18 is not afforded the priority date of the parent application, 08/066,371 (*see* below). However, the '021 patent is a divisional of 08/066,371 and, therefore, has the identical disclosure. It is not consistent that the claims of the '021 patent render present claim 18 obvious, but the disclosure of the '021 patent does not support this claim.

Regardless of the above, neither the claims of the '021 patent nor Yatani explicitly disclose forming heteromultimeric Kir3.0 channels. Therefore, neither the '021 patent claims

nor Yatani, individually or in combination, specifically disclose all of the elements of the present claims, as required.

In light of the discussion above, Applicants submit that Claims 18-20 are not obvious over the claims of the '021 patent in view of Yatani. Therefore, Applicants respectfully request withdrawal of this rejection.

Claims 21-24 are rejected under the judicially created doctrine of obviousness-type double patenting over claims 1-19 of the '021 patent in view of Duprat et al., *Biochem. Biophys. Res. Comm.* 212(2):657-663 (1995) (Duprat) and Yatani. Applicants respectfully traverse.

The requirements for a proper obviousness-type double patenting rejection are discussed above. Applicants point out that, *inter alia*, all of claims 21-24 have the element of introducing nucleic acid encoding a Kir3.0 channel formed from at least two different Kir3.0 polypeptides and expressing these nucleic acids in a host cell (Claims 21-22) or expression system (Claims 23-24).

As discussed above, the '021 patent does not have claims 1-19, nor do the claims of this patent explicitly disclose heteromultimeric Kir3.0 channels. Yatani does not disclose forming channels, nor does it discuss expression of any introduced nucleic acid in a host cell.

Duprat has a publication date of July 17, 1995. The front page of Duprat states that the article was "[r]eceived June 6, 1995".

Enclosed is an article entitled "Evidence that neuronal G-protein-gated inwardly rectifying K^+ channels are activated by $G\beta\gamma$ subunits and function as heteromultimers", *PNAS*, 92:6542-6546 (July 1995), by Paolo Kofuji, Norman Davidson and Henry Lester (Kofuji). These authors are the only named inventors of the present application. The publication date of this article is July 1995. The front page of this article states that the article was "[c]ontributed by Norman Davidson, April 10, 1995".

The enclosed article is evidence that the claimed subject matter was conceived prior to any disclosure by Duprat. Therefore, Duprat is not prior art which can be considered in determining the patentability of the present invention.

In light of the discussion above, Claims 21-24 are not obvious over the claims of the '021 patent in view of Yatani and Duprat. Therefore, Applicants respectfully request withdrawal of this rejection.

Priority

The Office Action raises the issue that the present Claim 18 may not be entitled to the priority date of the parent application, Serial No. 0/066,371. As Applicants have previously pointed out, unless the filing date of the earlier application is needed to overcome a reference, there is no need for such a determination to be made (*see* MPEP § 201.08). In this case, the present invention is non-obvious over all of the pertinent cited art; therefore the issue is moot. Furthermore, as noted above, the Office Action also suggests that the claims of a patent having the identical disclosure of the present parent application render present Claim 18 obvious. Since a reference must be enabling to be cited for an obviousness rejection, the Office Action suggests in the double patenting rejection what it refutes in the priority determination. As previously, applicants respectfully request that the consideration of priority be reserved until such time as a determination needs to be made.

Rejections Under 35 U.S.C. § 102

Claims 18-20 are rejected under 35 U.S.C. § 102(b) as being anticipated by Yatani. Applicants respectfully traverse.

For a rejection under 35 U.S.C. § 102 to be proper, each element of the rejected claim must be taught. The elements of Claims 18-20 are discussed above, as is the disclosure of Yatani. As discussed, Yatani does not disclose forming a functional Kir3.0 channel from at

least two different Kir3.0 polypeptides. For these reasons, Yatani does not anticipate Claims 18-20. Therefore, Applicants respectfully request that this 35 U.S.C. § 102(b) rejection be withdrawn.

Claims 18-20 are rejected under 35 U.S.C. § 102(b) as being anticipated by Karschin et al., *PNAS, USA* 88:5694-5698 (1991) (Karschin). Applicants respectfully traverse.

Karschin describes expression of heterologous serotonin receptors in heart cells and patch clamp recording from the membranes of these cells. Also as with Yatani, Karschin does not disclose forming a functional Kir3.0 channel from at least two different Kir3.0 polypeptides. Therefore, the claim element of providing a Kir3.0 channel formed from at least two different Kir3.0 polypeptides is not disclosed in Karschin.

For the reasons discussed above, Karschin does not anticipate Claims 18-20. Therefore, Applicants respectfully request that this 35 U.S.C. § 102(b) rejection be withdrawn.

Claims 18-24 are rejected under 35 U.S.C. § 102(a) as being anticipated by Duprat et al., *Biochem. Biophys. Res. Com.* 212(2):657-663 (1995) (Duprat). Applicants respectfully traverse.

Duprat has a publication date of July 17, 1995. The front page of Duprat states that the article was "[r]eceived June 6, 1995".

Enclosed is an article entitled "Evidence that neuronal G-protein-gated inwardly rectifying K^+ channels are activated by $G\beta\gamma$ subunits and function as heteromultimers", *PNAS*, 92:6542-6546 (July 1995), by Paolo Kofuji, Norman Davidson and Henry Lester (Kofuji). These authors are the only named inventors of the present application. The publication date of this article is July 1995. The front page of this article states that the article was "[c]ontributed by Norman Davidson, April 10, 1995".

The enclosed article is evidence that the claimed subject matter was conceived prior to any disclosure by Duprat. Therefore, Duprat is not prior art which can be considered in determining the patentability.

Furthermore, each of Claims 18-24 has the element of combining or contacting a candidate inhibitory agent with a functional Kir3.0 channel. As referenced by the Office Action mailed 3/15/00, Duprat discloses the requirement of Mg and ATP for the activity of various K+ channels (page 660-661, figure 2 and 4). Duprat neither discloses nor suggests agents that inhibit the Kir3.0 channels of the present claims, let alone a method for screening for such inhibitors. The present Office Action states, " . . . since the Mg and ATP blocks or inhibits the potassium current, it is an inhibitor." (Page 5, Point 11). Applicants point out that activity was decreased in the absence of MG or ATP. Therefore, neither of these "agents" was combined with the channels, but rather, they were removed from the channels. The element of combining a candidate inhibitor of a Kir3.0 channel is neither taught nor suggested by Duprat.

For the reasons discussed above, Duprat does not anticipate Claims 18-24. Therefore, Applicants respectfully request the withdrawal of this 35 U.S.C. § 102(a) rejection.

Applicants submit that the claims are in form for allowance and early notice of such is requested. If the Examiner believes that there are remaining issues which may be resolved by telephone, he is urged to call the undersigned at (415) 781-1989.

Respectfully submitted,

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VERSION SHOWING CHANGES MADE

18. (Twice Amended) A method for screening for agents that inhibit the activity of a Kir3.0 channel, the method comprising:

a) [providing] forming a functional Kir3.0 channel [formed] from at least two different inward rectifier, G-protein activated, mammalian, potassium Kir3.0 polypeptides;

b) combining the candidate agent with said Kir3.0 channel under conditions that permit inward K+ current;

c) determining the induced current, wherein a reduction in said induced current in the presence of said agent as compared to a control is indicative that said agent inhibits the activity of a Kir3.0 channel.

19. The method of Claim 18, wherein said Kir3.0 polypeptides are selected from the group consisting of polypeptides having at least about 50% amino acid sequence identity with Kir3.1, Kir3.2, Kir3.3 or Kir3.4.

20. The method of Claim 18, wherein said Kir3.0 polypeptides are selected from the group consisting of polypeptides encoded by nucleic acids that hybridize under low stringency conditions with a complement of a nucleic acid which encodes Kir3.1, Kir3.2, Kir3.3 or Kir3.4.

21. A method for screening for agents that inhibit the activity of a Kir3.0 channel, the method comprising:

a) providing a functional Kir3.0 channel formed by introducing into an expression host cell a nucleic acid encoding a first mammalian Kir3.0 polypeptide and a nucleic acid encoding a second mammalian Kir3.0 polypeptide under conditions that permit expression of said nucleic acid, wherein said first and second mammalian Kir3.0 polypeptides are different from each other, wherein said mammalian Kir3.0 polypeptides assemble to form a functional Kir3.0 in said expression host cell;

b) combining a candidate agent with a functional Kir3.0 channel under conditions that permit inward K+ current;

c) determining the induced current, wherein a decrease in said induced current in the presence of said agent as compared to a control is indicative that said agent inhibits the activity of a Kir3.0 channel.

22. The method of Claim 21, wherein said nucleic acid encoding said mammalian Kir3.0 polypeptides are selected from the group consisting of nucleic acids that hybridize under low stringency conditions with a complement of a nucleic acid which encodes Kir3.1, Kir3.2, Kir3.3 or Kir3.4.

23. A screening assay for identifying materials which inhibit the activity of a Kir3.0 channel, comprising the steps of:

(a) introducing nucleic acid encoding a Kir3.0 channel formed from at least two different inward rectifier, G-protein activated, mammalian, potassium Kir3.0 polypeptides into an expression system and causing the expression system to express said nucleic acid encoding a Kir3.0 channel;

(b) contacting the Kir3.0 channel with one or more candidate channel-inhibiting materials;

(c) selecting candidate material(s) which inhibit said activity relative to a control performed in their absence.

24. The method of Claim 23, wherein said nucleic acid encoding a Kir3.0 channel consists essentially of nucleic acids that hybridize under low stringency conditions with a complement of a nucleic acid which encodes Kir3.1, Kir3.2, Kir3.3 or Kir3.4.